Optimal Dose of Hypertonic Saline/Dextran in Hemorrhaged Swine

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Background: **Hypertonic saline/dextran (HSD) fluid resuscitation has been demonstrated to be effective in alleviating the adverse effects of hemorrhagic hypotension. The optimal dose of HSD has not been defined.**

Methods: **The comparative effectiveness of various dosages of HSD for the treatment of severe hemorrhage was investigated in conscious swine bled 46 mL/kg over 15 minutes, a lethal procedure. Five minutes after the completion of hemorrhage, animals were treated with 1, 2, 4, or 11.5 mL/kg HSD and observed over the next 96 hours.**

Results: **The 11.5-mL dose resulted in 100% survival, which was statistically superior to the 1- and 2-mL doses but not the 4-mL dose. Survival incidences with 4, 2, and 1 mL/kg were 83%, 64%, and 13%, respectively.**

Conclusion: **In terms of survival time, the 11.5- and 4-mL/kg doses were not significantly different. Therefore, optimum resuscitative effectiveness of HSD is achieved within the dose range of 4 to 11.5 mL/kg.**

Key Words: **Survival, Fluid resuscitation, Injury, Hypotension**

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Hypertonic saline/dextran (HSD) is now recognized as a highly effective resuscitation solution for the treatment of life-threatening hemorrhagic hypotension. The efficacy of HSD has been demonstrated in numerous animal models and in a number of clinical studies.[1–17] Administration of HSD (7.5% NaCl in 6% Dextran) corrects many of the hemodynamic and metabolic sequelae of hemorrhage, ultimately leading to an improvement in survival. Doses ranging from 2.5 to 11.5 mL/kg of HSD have been used.[2,18] Most of the studies in animals and humans, however, have used a dose of approximately 4 mL/kg of HSD. This dose has been shown to be efficacious, but was selected arbitrarily. As noted recently by Stern et al.,[19] to date there have been no definitive studies to determine the optimum dosage of HSD. The present study was conducted to addresses this question, presenting experimental data on the duration and incidence of survival after the administration of 1, 2, 4, or 11.5 mL/kg of HSD to conscious pigs that were subjected to an otherwise lethal controlled hemorrhage insult.[2,20]

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MATERIALS AND METHODS

All experimental procedures were reviewed and approved by the Institutional Animal Care and Use Committee at the Letterman Army Institute of Research, where the study was performed. Five days before experimental use, immature barrows and gilts, obtained from a commercial breeder (J.G. Boswell, Corcoran, CA) weighing 19 to 25 kg, were premedicated with 0.09 mg/kg atropine sulfate, 2.2 mg/kg ketamine hydrochloride, and 2.2 mg/kg xylazine administered intramuscularly. Halothane anesthesia was then induced (0.05% halothane, 1.0% methoxyflurane, nitrous oxide, and oxygen), and catheters were implanted under aseptic conditions in the left external jugular vein and descending aorta for infusion of the treatment solutions and blood withdrawal, respectively. The health and well-being of the animals were periodically assessed during the recovery period.

On the day of study, after an overnight fast with water available, each pig was transported to the laboratory and placed in a holding cage that restricted its movements. The conscious animal was then subjected to a 46-mL/kg hemorrhage over a 15-minute period, an insult that is fatal in over 87% of untreated pigs.[2,20] The animal was randomly assigned

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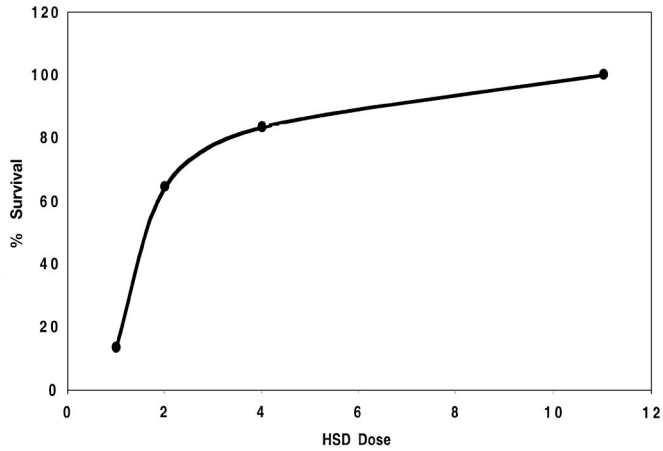

Fig. 1. *Percent survival of hemorrhaged swine treated with varying doses of HSD.*

to one of four groups and, 5 minutes after the completion of hemorrhage, treated with either 1, 2, 4, or 11.5 mL/kg of HSD, administered by rapid intravenous (jugular catheter) infusion. The resuscitation solution, 7.5% NaCl in 6% Dextran 70, was provided by Pharmacia, Inc. (Sweden; Batch I-328510). After resuscitation, the animals were observed for 3 hours and then returned to their cages, provided free access to food and water, and observed regularly over the next 96 hours. If death occurred, the duration of survival was recorded.

Statistical Analysis

Between-group resuscitative effectiveness in terms of survival versus nonsurvival during the 96-hour observation period was evaluated with a χ^2 test followed by Marascuilo's method of multiple comparisons.[21] Between-group resuscitative effectiveness in terms of survival time before death (or 96 hours if death did not occur) was evaluated with a generalized Wilcoxon test, after appropriate adjustments for multiple comparisons. Differences between mean values were considered significant when $p < 0.05$. Values in the text are means ± SEM. We used the PROBIT procedure in SAS[21] to conduct a quantal assay of the data to estimate the optimal dose for survival rates of 90% and 95%. The logistic distribution was used to estimate the parameters. A goodness-of-fit statistic is also reported.

RESULTS

All pigs resuscitated with 11.5 mL/kg of HSD (n = 14) were alive at the end of the 96-hour observation period, and resuscitative effectiveness of this dose was significantly superior to doses of 1 and 2 mL/kg, at least in terms of survival enhancement (Fig. 1). There was no significant difference in survival between 11.5 and 4 mL/kg. Resuscitation with 4 mL/kg of HSD (n = 18), and to a lesser extent 2 mL/kg (n = 14), also enhanced survival; respectively, 83% and 64% of the animals in these groups were alive at the end of the

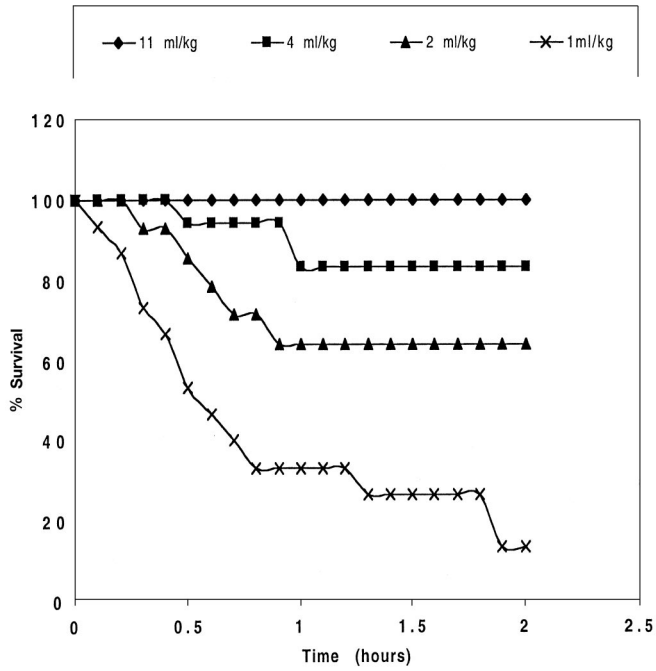

Fig. 2. *Percent survival over time of swine treated with varying doses of HSD. Animals were followed for 96 hours and no additional deaths occurred.*

observation period. In contrast, a 1-mL/kg dose (n = 15) was followed by only 13% survival, a value that was equal to that observed in this animal model when no resuscitative treatment was provided.[2]

Between-group comparisons of survival time after resuscitation also revealed significantly different dose effects (Fig. 2). As previously indicated, all animals treated with the 11.5-mL/kg dose survived the 96-hour observation period. Resuscitation with 4 mL/kg of HSD resulted in a mean survival time of 80 ± 10 hours, a value that was not significantly different from that observed after the 11.5-mL/kg dose. Survival time for the 2-mL/kg dose was 67 ± 13.8 hours, significantly less than the 11.5-mL/kg dose, but not different from the time observed with the 4-mL/kg dose. Animals receiving the 1-mL/kg dose survived 13 ± 8.7 hours, a value that was significantly less than observed with all other doses.

A quantal assay of the data estimated the optimal dose for 90% survival rate at 4.2 mL/kg (95 confidence interval, 3.28–7.30 mL/kg) and for 99% survival at 6.5 mL/kg (95% confidence interval, 4.82–12.75 mL/kg). A goodness-of-fit test based on the Pearson χ^2 suggested no lack of fit (p = 0.22) for the model.

DISCUSSION

On the basis of the data presented here, it appears that severely hemorrhaged swine can be effectively resuscitated with HSD at dosage levels of 3.3 to 7.3 mL/kg. The 4-mL/kg dose, although not 100% effective, did provide significant improvements in both the incidence and duration of survival

compared with lower doses and no treatment. Wade et al.[3] have previously shown that 4 mL/kg of HSD, in swine hemorrhaged over a longer period to end mean blood pressures similar to the model in the present study,[2] produced a survival rate of 66%, appreciably less that the 83% survival rate of the same dose in the present study. Velasco et al.[4] have reported a survival incidence of 92% in hemorrhaged anesthetized dogs that were administered 6 mL/kg of HSD. Stern et al.,[19] using a lethal model of uncontrolled hemorrhage in anesthetized swine, found administration of 8 mL/kg of HSD to improve survival to 75%, if the rate of infusion was slow. Thus, the experimental model and rate of infusion as well as the dose of HSD can influence the interpretation of survival data as indicated by studies of uncontrolled hemorrhage. In the present study, a consistent hemorrhage model was used that mimicked rapid blood loss and early (within 20 minutes of injury) fluid administration. The present study suggests that the dose of 4 mL/kg alone may not be fully effective for ensuring survival but does extend survival time after hemorrhage.

In the present animal studies, HSD was the only treatment solution administered. In the clinical setting, the administration of HSD has been followed by conventional fluids such as lactated Ringer's solution or normal saline.[7–14] The clinical dose presently recommended for HSD is 250 mL administered intravenously with additional fluids as deemed clinically necessary. This dose was selected arbitrarily on the basis of a number of factors. The first factor was the minimum fluid volume to be carried by military medics using available approved packaging (a 250-mL bag of solution that when administered to a 70-kg human was a dose of 3.6 mL/kg).[22] The second factor was based on the assumption that a greater dose of HSD would result in hypernatremia and neurologic dysfunction (the dose was calculated to maintain plasma sodium concentrations within a safe range).[6,23,24] The body weights of patients in previous studies of HSD have not been reported. From data records, we determined that the median body weight of patients enrolled in these studies was 72 kg (n = 519), with the resultant dose of HSD being approximately 3.5 mL/kg.[16] In addition, in the majority of these patients, plasma sodium concentrations, although elevated, were within the desired safety range.[7–14] After treatment with HSD, 90% of the patients had plasma sodium levels less than 155 mmol/L.[10,16] A dose of 250 mL of HSD is effective in expanding blood volume[25] to a greater extent than an equal volume of normal saline solutions and in correcting the hypotension observed in trauma patients.[12] The presently recommended clinical dose of HSD (250 mL), therefore, is within the effective range for expanding blood volume and correcting blood pressure in the patient with traumatic injuries and hypotension. However, this dosage, if administered as the sole resuscitation solution, may be below the level that could ensure a maximal advantage for survival.

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